Exhibit A

Guidance for FDA Staff and Industry

Marketed Unapproved Drugs — Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without Approved NDAs or ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006

Compliance

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006

Compliance

Contains Nonbinding Recommendations

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Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This compliance policy guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This CPG supersedes section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02). It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Reason for This Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the Act) or remove the products from the market. We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.

The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

B. Historical Enforcement Approach

FDA estimates that, in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval.[2] Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action. Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts and exercise enforcement discretion with regard to products that remain on the market.

In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has either come to our attention during inspections or been brought to our attention by outside sources.

III. FDA'S ENFORCEMENT POLICY

In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement actions and exercising our enforcement discretion with regard to the universe of unapproved, illegally marketed drug products in all categories.

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[2] This rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers.

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A. Enforcement Priorities

Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to continue its current policy of giving higher priority to enforcement actions involving unapproved drug products in the following categories:

Drugs with potential safety risks. Removing potentially unsafe drugs protects the public from direct and indirect health threats.

Drugs that lack evidence of effectiveness. Removing ineffective drugs protects the public from using these products in lieu of effective treatments. Depending on the indication, some ineffective products would, of course, pose safety risks as well.

Health fraud drugs. FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in this area are drugs that present a direct risk to health. Indirect health hazards exist if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. Indirect health hazards will be evaluated for enforcement action based on section 120.500, Health Fraud - Factors in Considering Regulatory Action (CPG 7150.10). FDA's health fraud CPG outlines priorities for evaluating regulatory actions against indirect health hazard products, such as whether the therapeutic claims are significant, whether there are any scientific data to support the safety and effectiveness of the product, and the degree of vulnerability of the prospective user group (CPG Sec. 120.500).

Drugs that present direct challenges to the new drug approval and OTC drug monograph systems. The drug approval and OTC drug monograph systems are designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. The drugs described in the preceding three categories present direct challenges to these systems, as do unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval (*see* section III.C., Special Circumstances – Newly Approved Product). Also included are drugs marketed in violation of a final and effective OTC drug monograph. Targeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health.

Unapproved new drugs that are also violative of the Act in other ways. The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug

made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation *and* the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. *See United States v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

Drugs that are reformulated to evade an FDA enforcement action. The Agency is also aware of instances in which companies that anticipate an FDA enforcement action against a specific type or formulation of an unapproved product have made formulation changes to evade that action, but have not brought the product into compliance with the law. Companies should be aware that the Agency is not inclined to exercise its enforcement discretion with regard to such products. Factors that the Agency may consider in determining whether to bring action against the reformulated products include, but are not limited to, the timing of the change, the addition of an ingredient without adequate scientific justification (*see, e.g.*, 21 CFR 300.50 and 330.10(a)(4)(iv)), the creation of a new combination that has not previously been marketed, and the claims made for the new product.

B. Notice of Enforcement Action and Continued Marketing of Unapproved Drugs

FDA is not required to, and generally does not intend to, give special notice that a drug product may be subject to enforcement action, unless FDA determines that notice is necessary or appropriate to protect the public health.[3] The issuance of this guidance is intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.[4] The only exception to this policy is, as set forth elsewhere, that generally products subject to an ongoing DESI[5] proceeding or ongoing OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place) may remain on the market during the pendency of

[3] For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and requiring manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24488, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

[4] For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its *grandfather* status (21 U.S.C. 321(p)).

[5] The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

that proceeding[6] and any additional period specifically provided in the proceeding (such as a delay in the effective date of a final OTC drug monograph).[7] However, once the relevant DESI or OTC drug monograph proceeding is completed and any additional grace period specifically provided in the proceeding has expired, all products that are not in compliance with the conditions for marketing determined in that proceeding are subject to enforcement action at any time without further notice (*see, e.g.*, 21 CFR 310.6).

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period,[8] we may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration.

C. Special Circumstances — Newly Approved Product

Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[9] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.

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[6] OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies. *See, e.g.*, CPG sections 450.200 and 450.300 and 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

[7] Sometimes, a final OTC drug monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph are subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

[8] For purposes of this guidance, the terms *grace period* and *allow a grace period* refer to an exercise of enforcement discretion by the Agency (i.e., a period of time during which FDA, as a matter of discretion, elects not to initiate a regulatory action on the ground that an article is an unapproved new drug).

[9] These may be products that are the same as the approved product or somewhat different, such as products of different strength.

When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed;[10] (3) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first cease *manufacturing* unapproved forms of the drug product, and later cease *distributing* the unapproved product.

The length of any grace period and the nature of any enforcement action taken by FDA will be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not be sent before initiation of enforcement action and should not expect any grace period that is granted to protect them from the need to leave the market for some period of time while obtaining approval. Companies marketing unapproved new drugs should also recognize that, while FDA normally intends to allow a grace period of roughly 1 year from the date of approval of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction) against others who are marketing that unapproved product, it is possible that a substantially shorter grace period would be provided, depending on the individual facts and circumstances.[11]

The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. For example, if FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer.

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[10] For example, at the Agency's discretion, we may provide for a shorter grace period if an applicant seeking approval of a product that other companies are marketing without approval agrees to publication, around the time it submits the approval application, of a *Federal Register* notice informing the public that the applicant has submitted that application. A shortened grace period may also be warranted if the fact of the application is widely known publicly because of applicant press releases or other public statements. Such a grace period may run from the time of approval or from the time the applicant has made the public aware of the submission, as the Agency deems appropriate.

[11] Firms are reminded that this CPG does not create any right to a grace period; the length of the grace period, if any, is solely at the discretion of the Agency. For instance, firms should not expect any grace period when the public health requires immediate removal of a product from the market, or when the Agency has given specific prior notice in the *Federal Register* or otherwise that a drug product requires FDA approval.

FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.[12]

D. Regulatory Action Guidance

District offices are encouraged to refer to CDER for review (with copies of labeling) any unapproved drugs that appear to fall within the enforcement priorities in section III.A. Charges that may be brought against unapproved drugs include, but are not limited to, violations of 21 U.S.C. 355(a) and 352(f)(1) of the Act. Other charges may also apply based on, among others, violations of 21 U.S.C. 351(a)(2)(B) (CGMP), 352(a) (misbranding), or 352(o) (failure to register or list).

[12] The Agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the Agency will provide relevant information on the matter to the Federal Trade Commission (FTC). In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications (ANDAs), citizen petitions, and scientific challenges to the approval of competitor drug products.

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APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL[13]

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (*see* 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a *new drug* also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as *safe* between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow

[13] This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular drug or category of drugs, the original source documents cited should be consulted.

procedures in the Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.
- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register*.
- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs, as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.
- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action.

1. Products Subject to Ongoing DESI Proceedings

Some unapproved marketed products are undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (i.e., those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related, or similar to those products specifically reviewed (*see* 21 CFR 310.6). In virtually all these proceedings, FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. It is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding. *See, e.g., Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D. Mich. 1969).[14]

2. Products Subject to Completed DESI Proceedings

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This group also includes a number of products IRS to those DESI products for which FDA made a

[14] Products first marketed after a hearing notice is issued with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing. Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. *See, e.g.*, "Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy" (DESI 6514), 49 FR 153 (January 3, 1984) (Dimetane and Actifed); "Certain Drugs Containing Antibiotic, Corticosteroid, and Antifungal Components" (DESI 10826), 50 FR 15227 (April 17, 1985) (Mycolog). *See also* 21 U.S.C. 356a(c)(2)(A). Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.

final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy (*see* 21 CFR 310.6). FDA considers all products described in this paragraph to be marketed illegally.

C. Prescription Drug Wrap-Up

As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of these, many claimed to have been marketed prior to 1938 or to be IRS to such a drug. Drugs that did not have pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to DESI. For a period of time, FDA did not take action against these drugs and did not take action against new unapproved drugs that were IRS to these pre-1962 drugs that entered the market without approval.

Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a congressional oversight committee issued a report to FDA expressing the committee's concern regarding the thousands of unapproved drug products in the marketplace.

In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed drug products. To address those drug products, the Agency significantly revised and expanded CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI products. The program for addressing these marketed unapproved drugs and certain others like them became known as the *Prescription Drug Wrap-Up*. Most of the Prescription Drug Wrap-Up drugs first entered the market before 1938, at least in some form. For the most part, the Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription Drug Wrap-Up.

A drug that was subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer of such a drug can establish that its drug is grandfathered or otherwise not a *new drug*.

Under the 1938 grandfather clause (*see* 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that Act was not considered a *new drug* and therefore was exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application. *See* Pub. L. 87-781, section 107 (reprinted following 21 U.S.C.A. 321); *see also USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

The two grandfather clauses in the Act have been construed very narrowly by the courts. FDA believes that there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. *See* 21 CFR 314.200(e)(5); *see also United States v. An Article of Drug (Bentex Ulcerine),* 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).

Finally, a product would not be considered a *new drug* if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. *See* 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. *See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *United States v. 50 Boxes More or Less Etc.*, 909 F.2d 24, 27-28 (1st Cir. 1990); *United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409 (3rd Cir. 1989). *See also* Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE).

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at least theoretically possible. No part of this guidance, including the Appendix, is a finding as to the legal status of any particular drug product. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

D. New Unapproved Drugs

Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the market illegally. Some also may have already been the subject of a formal Agency finding that they are new drugs. *See, e.g.*, 21 CFR 310.502 (discussing, among other things, controlled/timed release dosage forms).

E. Over-the-Counter (OTC) Drug Review

Although OTC drugs were originally included in DESI, FDA eventually concluded that this was not an efficient use of resources. The Agency also was faced with resource challenges because it was receiving many applications for different OTC drugs for the same indications. Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process involves convening an advisory panel for each therapeutic class to review data relating to claims and active ingredients. These panel reports are then published in the *Federal Register*, and after FDA review, tentative final monographs for the classes of drugs are published. The final step is the publication of a final monograph for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class (*see, e.g.*, 21 CFR part 333). Drugs marketed in accordance with a final monograph are considered to be generally recognized as safe and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

Final monographs have been published for the majority of OTC drugs. Tentative final monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a number of *negative monographs* that list therapeutic categories (*e.g.*, OTC daytime sedatives, 21 CFR 310.519) in which no OTC drugs can be marketed without approval. Finally, the Agency has promulgated a list of active ingredients that cannot be used in OTC drugs without approved applications because there are inadequate data to establish that they are GRAS/GRAE (*e.g.*, phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies (*see, e.g.*, CPG sections 450.200 and 450.300, and 21 CFR part 330). This document does not affect the current enforcement policies for such drugs.

OTC drugs that need approval, either because their ingredients or claims are not within the scope of the OTC drug review or because they are not allowed under a final monograph or another final rule, are illegally marketed. For example, this group would include a product containing an ingredient determined to be ineffective for a particular indication or one that exceeds the dosage limit established in the monograph. Such products are new drugs that must be approved by FDA to be legally marketed.

Exhibit B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

March 30, 2009

Arthur P. Bedrosian, J.D., President
Lannett Company, Inc.
9000 State Road
Philadelphia, PA 19136

Products:
Morphine Sulfate Solution Immediate Release 20mg/ml;
Hydromorphone HCl Tablets, 2mg and 4mg

Dear Mr. Bedrosian:

This letter is written in reference to your firm's marketing of unapproved new drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act). Based on the information your firm submitted to FDA's Drug Registration and Listing System, you manufacture and distribute the following prescription drugs:

- Morphine Sulfate Solution Immediate Release 20mg/ml;
- Hydromorphone HCl Tablets, 2mg and 4mg

As labeled, the above products are drugs within the meaning of section 201(g)(1)(B) and (C) of the Act [21 U.S.C. §§ 321(g)(1)(B) and (C)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and because they are intended to affect the structure or function of the body. Further, these drug products as manufactured and distributed by your firm are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the product. Based upon our information, there are no FDA-approved applications on file for the above products. The marketing of these products without an approved application constitutes a violation of these provisions of the Act.

Additionally, because the above products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate

directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(l) of the Act [21 U.S.C. § 352(f)(1)]. Because your products lack required approved applications, they are not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these products therefore violates sections 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and (d)].

As described in the guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide"[1] the Agency may exercise its enforcement discretion and identify a period of time during which the Agency does not intend to initiate an enforcement action against a currently marketed unapproved drug. FDA does not intend to initiate enforcement actions related to your unapproved drug products, Morphine Sulfate Solution Immediate Release 20mg/ml and Hydromorphone HCl Tablets, 2mg & 4mg, that are being manufactured as of the date of this letter, unless the manufacturing of these products continues more than 60 days after the date of this letter. Furthermore, FDA does not intend to initiate enforcement actions related to the shipment in interstate commerce of these products unless they are still being shipped more than 90 days after the date of this letter.

You should be aware that FDA's enforcement discretion will not apply to the following circumstances: (1) if FDA determines that your firm is violating other provisions of the Act; (2) if it appears that your firm, in response to this letter, increases its manufacture or distribution of your unapproved products, Morphine Sulfate Solution Immediate Release 20mg/ml and Hydromorphone HCl Tablets, 2mg, & 4mg, above your usual volume during these periods; or (3) if FDA learns of new information regarding any serious health risk or hazard associated with morphine sulfate or hydromorphone hydrochloride drug products.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist in connection with your products. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of Federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other Federal agencies may take this Warning Letter into account when considering the award of contracts.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing regarding whether you plan to cease the violative activities described in this letter. If you no longer manufacture or market the products referenced in this letter, your response should so indicate, including the reasons that, and the date on which, you ceased production. Additionally, if another firm manufactures the products identified above, your reply should include the name

[1] Marketed Unapproved Drugs—Compliance Policy Guide. Available at http://www.fda.gov/cder/guidance/6911fnl.pdf

and address of the manufacturer. If the firm from which you receive these products is not the manufacturer, please include the name of your supplier in addition to the manufacturer.

Your response to this letter should be directed to the attention of Ms. Sakineh Walther, Consumer Safety Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, WO51 RM 5242, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,

/s/

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Exhibit C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

March 30, 2009

Richard E. Asherman, CEO
Cody Laboratories, Inc.
601 Yellowstone Avenue
Cody, Wyoming 82414

Product:
Morphine Sulfate Solution Immediate Release 20mg/ml

Dear Mr. Asherman:

This letter is written in reference to your firm's marketing of an unapproved new drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act). Based on the information your firm submitted to FDA's Drug Registration and Listing System, you manufacture the following prescription drug:

- Morphine Sulfate Solution Immediate Release 20mg/ml

As labeled, the above product is a drug within the meaning of section 201(g)(1)(B) and (C) of the Act [21 U.S.C. §§ 321(g)(1)(B) and (C)] because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and because it is intended to affect the structure or function of the body. Further, this drug product as manufactured by your firm is a "new drug" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because it is not generally recognized as safe and effective for its labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the product. Based upon our information, there is no FDA-approved application on file for the above product. The marketing of this product without an approved application constitutes a violation of these provisions of the Act.

Additionally, because the above product is intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for it so that a layman can use this product safely for its intended uses.

Consequently, its labeling fails to bear adequate directions for its intended uses, causing it to be misbranded under section 502(f)(l) of the Act [21 U.S.C. § 352(f)(1)]. Because your product lacks a required approved application, it is not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of this product therefore violates sections 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and (d)].

As described in the guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide"[1] the Agency may exercise its enforcement discretion and identify a period of time during which the Agency does not intend to initiate an enforcement action against a currently marketed unapproved drug. FDA does not intend to initiate enforcement actions related to your unapproved drug product Morphine Sulfate Solution Immediate Release 20mg/ml, that is being manufactured as of the date of this letter, unless the manufacturing of this product continues more than 60 days after the date of this letter. Furthermore, FDA does not intend to initiate enforcement actions related to the shipment in interstate commerce of this product unless it is still being shipped more than 90 days after the date of this letter.

You should be aware that FDA's enforcement discretion will not apply to the following circumstances: (1) if FDA determines that your firm is violating other provisions of the Act; (2) if it appears that your firm, in response to this letter, increases its manufacture or distribution of your unapproved product, Morphine Sulfate Solution Immediate Release 20mg/ml, above your usual volume during these periods; or (3) if FDA learns of new information regarding any serious health risk or hazard associated with morphine sulfate drug products.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist in connection with your product. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of Federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other Federal agencies may take this Warning Letter into account when considering the award of contracts.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing regarding whether you plan to cease the violative activities described in this letter. If you no longer manufacture or market the product referenced in this letter, your response should so indicate, including the reasons that, and the date on which, you ceased production. Additionally, if another firm manufactures the product identified above, your reply should include the name and address of the manufacturer. If the firm from which you receive this product is not the manufacturer, please include the name of your supplier in addition to the manufacturer.

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[1] Marketed Unapproved Drugs—Compliance Policy Guide. Available at http://www.fda.gov/cder/guidance/6911fnl.pdf

Your response to this letter should be directed to the attention of Ms. Sakineh Walther, Consumer Safety Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, WO51 RM 5242, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,

/s/

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Exhibit D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

April 9, 2009

Arthur P. Bedrosian, J.D., President
Lannett Company, Inc.
9000 State Road
Philadelphia, PA 19136

Product:
Morphine Sulfate Solution Immediate Release 20 mg/ml

Dear Mr. Bedrosian:

This letter is written in reference to the March 30, 2009 warning letter (Warning Letter) your firm received for /distributing morphine sulfate oral solution 20 mg/ml, an unapproved new drug, in violation of the Federal Food, Drug, and Cosmetic Act (the Act).

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to assure that safe and effective drugs are available to the American people. The drug approval system is one of the essential means by which CDER achieves its mission and ensures that patients have access to prescription drugs of proven safety, efficacy, and quality.

FDA remains committed to taking enforcement actions against unapproved drugs in an effort to ensure that drugs used by patients are safe and effective, while at the same time ensuring that such actions do not impose an undue burden on patients. Currently, there are no approved morphine sulfate oral solution 20 mg/ml products being marketed in the U.S. FDA has heard from the pain management community that the impending market removal of unapproved morphine sulfate oral solution 20 mg/ml products announced in the Warning Letter would impose extreme hardship on palliative care patients and their families. In light of this information, FDA intends to extend the period of enforcement discretion set forth in the Warning Letter to ensure that palliative care patients have access to morphine sulfate oral solution 20 mg/ml.

The period of enforcement discretion set forth in the Warning Letter will be extended until 180 days after any firm receives approval for a morphine sulfate oral solution 20 mg/ml product. If your firm [manufacturers/distributes] an unapproved morphine sulfate oral solution 20 mg/ml beyond the date that is 180 days after the date of such an approval, that activity may result in legal action without further notice, including, without limitation, seizure and injunction. The

extension of this period of enforcement discretion will not apply if FDA determines that your firm is violating other provisions of the Act or identifies additional safety information, or if FDA determines that alternative medications become available that could meet the needs of palliative care patients. FDA is actively evaluating alternatives to morphine sulfate oral solution 20 mg/ml and working with firms to expedite approval of such products. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations. Please be advised that we are not extending the period of enforcement discretion for any other products identified in the Warning Letter; the period of enforcement discretion stated in the Warning Letter will continue to apply to those other products.

Furthermore, FDA reiterates its expectation that all firms that market unapproved drugs to the American public submit the required applications to obtain approval for those products. FDA intends to continue to take aggressive enforcement action against marketed unapproved drugs.

FDA understands the need to continue to provide assistance to firms and to help them secure approval for unapproved drugs they are currently marketing. As part of this commitment, FDA appointed an unapproved drugs coordinator in the Office of New Drugs, Dr. Sally Loewke, to work with companies trying to bring their products into compliance. Please contact Parinda Jani, Chief Project Manager, Office of New Drugs, at 301-796-1232, about obtaining the necessary approval for your unapproved morphine sulfate oral solution 20 mg/ml drug product or any other unapproved product you may be marketing.

FDA is committed to making sure that patients have access to drugs of proven safety, efficacy, and quality and hopes that your firm shares this same commitment. If you have any additional questions concerning this letter, please contact Ms. Sakineh Walther, Compliance Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, HFD-310, WO51 RM 542, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Exhibit E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

April 9, 2009

Richard E. Asherman, CEO
Cody Laboratories, Inc.
601 Yellowstone Avenue
Cody, Wyoming 82414

Product:
Morphine Sulfate Solution Immediate Release 20mg/ml

Dear Mr. Asherman:

This letter is written in reference to the March 30, 2009 warning letter (Warning Letter) your firm received for manufacturing morphine sulfate oral solution 20 mg/ml, an unapproved new drug, in violation of the Federal Food, Drug, and Cosmetic Act (the Act).

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to assure that safe and effective drugs are available to the American people. The drug approval system is one of the essential means by which CDER achieves its mission and ensures that patients have access to prescription drugs of proven safety, efficacy, and quality.

FDA remains committed to taking enforcement actions against unapproved drugs in an effort to ensure that drugs used by patients are safe and effective, while at the same time ensuring that such actions do not impose an undue burden on patients. Currently, there are no approved morphine sulfate oral solution 20 mg/ml products being marketed in the U.S. FDA has heard from the pain management community that the impending market removal of unapproved morphine sulfate oral solution 20 mg/ml products announced in the Warning Letter would impose extreme hardship on palliative care patients and their families. In light of this information, FDA intends to extend the period of enforcement discretion set forth in the Warning Letter to ensure that palliative care patients have access to morphine sulfate oral solution 20 mg/ml.

The period of enforcement discretion set forth in the Warning Letter will be extended until 180 days after any firm receives approval for a morphine sulfate oral solution 20 mg/ml product. If your firm manufacturers an unapproved morphine sulfate oral solution 20 mg/ml beyond the date that is 180 days after the date of such an approval, that activity may result in legal action without

further notice, including, without limitation, seizure and injunction. The extension of this period of enforcement discretion will not apply if FDA determines that your firm is violating other provisions of the Act or identifies additional safety information, or if FDA determines that alternative medications become available that could meet the needs of palliative care patients. FDA is actively evaluating alternatives to morphine sulfate oral solution 20 mg/ml and working with firms to expedite approval of such products. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations. Please be advised that we are not extending the period of enforcement discretion for any other products identified in the Warning Letter; the period of enforcement discretion stated in the Warning Letter will continue to apply to those other products.

Furthermore, FDA reiterates its expectation that all firms that market unapproved drugs to the American public submit the required applications to obtain approval for those products. FDA intends to continue to take aggressive enforcement action against marketed unapproved drugs.

FDA understands the need to continue to provide assistance to firms and to help them secure approval for unapproved drugs they are currently marketing. As part of this commitment, FDA appointed an unapproved drugs coordinator in the Office of New Drugs, Dr. Sally Loewke, to work with companies trying to bring their products into compliance. Please contact Parinda Jani, Chief Project Manager, Office of New Drugs, at 301-796-1232, about obtaining the necessary approval for your unapproved morphine sulfate oral solution 20 mg/ml drug product or any other unapproved product you may be marketing.

FDA is committed to making sure that patients have access to drugs of proven safety, efficacy, and quality and hopes that your firm shares this same commitment. If you have any additional questions concerning this letter, please contact Ms. Sakineh Walther, Compliance Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, HFD-310, WO51 RM 542, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Exhibit F

ALSTON&BIRD LLP

The Atlantic Building
950 F Street, NW
Washington, DC 20004-1404

202-756-3300
Fax:202-756-3333
www.alston.com

Marc J. Scheineson Direct Dial: 202-756-3465 E-mail: marc.scheineson@alston.com

May 1, 2009

VIA E-MAIL (sakineh.walther@fda.hhs.gov)
(Original Sent Via Overnight Mail)

Not For Public Disclosure
Contains Confidential
Commercial Information

Ms. Sakineh Walther
Consumer Safety Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
W051 RM5242
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Response to Warning Letter to Lannett Company, Inc.

Dear Ms. Walther:

On behalf of the Lannett Company, Inc. ("Lannett"), we are responding to the above-captioned Warning Letter dated March 30, 2009 issued by Deborah M. Autor, Esq., Director, Office of Compliance. This response is due on May 1, 2009 pursuant to an understanding with the Division of New Drugs and Labeling Compliance (the Division). We also acknowledge and appreciate the opportunity to meet directly with the Agency on April 15, 2009 to discuss the issues raised herein. A copy of our Minutes from the meeting are included in this response as Attachment "A."

I. Background

The Warning Letter contends that two prescription drugs marketed by Lannett are "new drugs" that have not been reviewed and approved by the U.S. Food and Drug Administration ("FDA"). According to FDA, these drugs, therefore, may not be introduced or delivered for introduction into interstate commerce in the absence of an approved new drug application ("NDA") or abbreviated new drug application ("ANDA"). In the absence of such an approval, the Warning Letter also contends that the products fail to bear adequate directions for use and are misbranded.

The two Lannett products that are the subject of the Warning Letter are:

- Morphine Sulfate Solution Immediate Release, 20 mg/ml;

- Hydromorphone HCI Tablets, 2 mg and 4 mg

Please note that the morphine product is manufactured for Lannett by Cody Laboratories, Inc. ("Cody"), Cody, Wyoming. Cody received a similar Warning Letter requesting that it also discontinue production and marketing of Morphine Sulfate within 60-days. Its response is also due by May 1. We also represent Cody in this matter and will be responding separately.

The Warning Letter to Lannett is one of nine warning letters issued by FDA at the same time regarding drug products containing Morphine Sulfate, Hydromorphone, or Oxycodone, as part of its "unapproved drugs" initiative set forth in Compliance Policy Guide Section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs ("CPG"), available at http://www.fda.gov/cder/guidance/6911fnl.pdf.

Since the Warning Letters were issued on March 30, 2009, and as Lannett had discussed with the Division, FDA discovered that the concentrated Morphine Sulfate solution (20 mg/ml) manufactured and marketed by Lannett and Cody Labs was indispensible in the palliative care community. In order to prevent shortages and hoarding of existing supplies, FDA agreed to modify its announced decision to remove unapproved products from the market, utilizing its enforcement discretion. FDA announced that this product can remain on the market until 180 days following the date an approved product, or viable alternative, is available on the market (see http://www.fda.gov/cder/drug/unapproved_drugs/morphine_extension.htm). At FDA's request, Lannett has also worked to increase the production and distribution of Morphine Sulfate concentrate solution to meet existing demand making up for production lost when the drugs of KV Pharmaceuticals were removed from the marketplace.

Lannett continues to work with the Agency to prepare, organize and submit the data FDA needs to insure the continued safe and effective use of these products. These actions are described below. At the same time, in Lannett's defense, the following facts need to be presented for the Agency's review and consideration:

(1) Its morphine and Hydromorphone products are lawfully marketed based on their "grandfather" status, and the "new drug" requirements are not applicable.

(2) In any event, as discussed herein, Lannett has had ANDAs for Hydromorphone pending with the Office of Generic Drugs (OGD) since 2004, and expects to be able to submit a Section 505(b)(2) NDA for Morphine Sulfate by the end of 2009.

(3) Review of the history of the two Lannett products demonstrates that neither meets the CPG trigger points for taking this type of enforcement action demanding that all manufacturing cease immediately, and not later than May 29, 2009 (60 days from the date of the Warning Letter). The Warning Letter should be rescinded or modified, within FDA's enforcement discretion, to permit continued manufacture and marketing as long as applications have been submitted to FDA and accepted for filing and as requested in this response.

II. Morphine Sulfate Is Not a New Drug

In its CPG, FDA recognizes the possibility that a currently marketed prescription drug is grandfathered or is otherwise not a new drug. Id. at p. 11. As FDA explained in the CPG, there are two grandfather provisions that helped make up the current Food Drug and Cosmetic Act (the Act). Under the 1938 grandfather clause, 21 U.S.C. §321(p)(1), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling "the same representations concerning the conditions of its use" as it did prior to passage of that Act was not considered a new drug. It, therefore, remains exempt from the requirement of maintaining an approved new drug application. Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, prior to enactment of the 1962 amendments, it was: (a) used or sold commercially in the U.S.; (b) was not a new drug; and (c) was not covered by an effective NDA, *see* CPG at page 10 and Public L. 87-781, section 107, reprinted following 21 U.S.C. §321.

Concededly, both FDA and the few relevant court decisions construed these grandfather provisions narrowly. However, it is important to recognize that the 1962 provision is more restrictive than the 1938 clause. The former calls for a comparison of the drug products' conditions of use, composition and labeling, while the 1938 clause focuses only on a comparison of their conditions of use. Even though the courts and FDA have narrowly interpreted grandfather status, the Lannett morphine products still fall within even the most narrow interpretations. Morphine was available well before 1938 in morphine sulfate form in numerous sizes and configurations and that is well documented.

The distinction between the pre-38 and pre-62 products is also critical in assessing the regulatory status of a very old drug like Morphine Sulfate. Lannett and Cody have maintained and shared historical files regarding the marketing and labeling of the product. Those records, which have been available for inspection by FDA, and have been offered to FDA investigators on numerous occasions, demonstrate that undiluted immediate release Morphine Sulfate solution has been commercially sold and marketed in the United States since at least 1900 , well before enactment of the 1938 Act. Its conditions of use (for the relief of severe acute and severe chronic pain) have not changed since that time. Please note, for example, the attached excerpt from the 1936 U.S. Pharmacopoeia (Attachment "B") reflecting that Morphine Sulfate (oral solutions and tablets) were contained on its official list of "Pre-1938" products. During this early period, Morphine Sulfate was normally compounded by pharmacists to order at various strengths based on the needs of the patient (e.g., morphia powder, distilled water and diluted sulphuric acid). The notebook of original historical documents contained in Lannett's offices (which we are happy to copy and send to you at your request) definitively demonstrates that the drug was on the market for the same use. This is the extent of Lannett's burden of proof under 21 U.S.C. §321(p)(1). Accordingly, Lannett's Morphine Sulfate is not a new drug and may be lawfully manufactured and marketed in the absence of an approved application.

Despite our legal opinion to Lannett that its Morphine Sulfate solution is one of only a very few current drugs legally grandfathered under the 1938 Act, Lannett has opted to prepare a NDA application under §505(b)(2) of the Act. This action was requested (demanded) by FDA during our meeting on April 15, 2009. Following that meeting, Lannett reached out to the CDER Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) on April 21, 2009 via email to Ms. Parinda Jani as directed. Mr. Ernest Sabo, Lannett Vice President, Regulatory and Corporate Compliance, requested a face-to-face pre-IND meeting to discuss the elements of the application. A follow-up letter was provided fulfilling the regulatory requirements of a Pre-IND Review Request. Six-months of accelerated stability data and a preservative study was included in the request letter. On April 29, 2009, Ms. Jani responded that she was "setting up a teleconference with Lannett in June." Certainly, given the extreme time limitations created by FDA in its exercise of its enforcement discretion (which could be as short as 6 months), it is the responsibility of the review division to prioritize this process. That does not appear to be happening.

It is only rational and reasonable under these circumstances that FDA would permit a product, for which safety or efficacy have not been questioned, to remain on the market if a complete application has been received by FDA and accepted for filing prior to the enforcement deadline. This is especially true if, as you stated on April 15, 2009, the purpose of issuing the Warning Letters was to obtain data from the manufacturer, and not to remove existing drugs from the market where a shortage already exists. Lannett cannot control the pace of FDA application review, and FDA likely does not want to create additional pressure on its review staff. Therefore, Lannett requests FDA to exercise its enforcement discretion to maintain its Morphine Sulfate solution (20 mg/ml) on the market as long as a complete §505(b)(2) NDA is provided to the Agency no later than December 31, 2009 (180 days from the likely date of approval of the first NDA). Lannett will try to complete the application as expeditiously as possible before that date.

III. Hydromorphone HCl

Notwithstanding its belief that Hydromorphone HCl is also lawfully marketed under the grandfather provisions of the Act, at FDA's suggestion, Lannett previously submitted two ANDAs to FDA as follows:

A. ANDA 77-471 for Hydromorphone HCl, 8 mg., submitted on December 22, 2004, amended on February 27 and June 12, 2007.

B. ANDA 78-439 for Hydromorphone HCl, 2 mg. and 4 mg., submitted on May 3, 2006 and amended on February 27 and June 12, 2007.

Given the pendency of those applications at the Agency, it is difficult to understand why these drugs were the subject of a Warning Letter to Lannett.

For both applications, Cody Labs in Cody, Wyoming, was listed as the manufacturer of the active pharmaceutical ingredient (API). Some of the delay in approval of these applications is likely attributable to reassignments of Agency personnel responsible for review of the ANDAs, and to problems encountered by Cody in maintaining compliance with current manufacturing practices (cGMPs). Eventually, in April 2007, Cody was reinspected by FDA in response to an April 2006 Warning Letter issued by the Denver District Office. The results of that reinspection were reportedly satisfactory. A Form 483 was issued, but included four relatively minor observations, all of which were promptly corrected.

The District, however, reportedly believes that before the preapproval inspection can be completed, and the ANDAs approved, the inspectors need to revisit the plant in Cody, Wyoming to visually inspect the API actually being produced (v. reviewing batch records). At the same time that reinspection assignment was seemingly deferred when OGD sent letters to Lannett in December 2007 finding both ANDAs to be "not approvable" due to cGMP deficiencies at Cody.

This seemed to create a "Catch 22" for Lannett. The ANDAs could not be approved without the reinspection, yet the reinspection could not occur if the ANDAs were not being actively reviewed. Further, as was evident during our recent April 15 meeting, there is also some reluctance by the District to commit to assigning an inspector timely to Cody once Cody reports that it is in production. After further discussion during the meeting, it appears that, once Cody provides advance notice of when it will resume production of Hydromorphone, the District will either inspect during that time, or else promptly inspect the resulting documentation (batch records). Hopefully, this understanding will lead to prompt approvals since, as was acknowledged by FDA at the meeting, there are no remaining issues with respect to the Hydromorphone ANDAs, other than the final inspection visit to Cody (or review of batch records for the API).

Lannett respectfully requests that FDA approve the ANDAs, based on Cody's recent inspection. In the alternative, we hope that you will work with Lannett and Cody to ensure that API, or batch records for the most recent production run, will be reviewed as expeditiously as possible so that approvals can be issued before the Warning Letter demand that all manufacturing cease no later than May 29, 2009 unless an application is approved.

IV. FDA Should Defer Enforcement Action

The stated purpose of the CPG was to describe how FDA intended to exercise its enforcement discretion with regard to prescription (Rx) drugs marketed in the US that do not have FDA marketing approval. Concededly, FDA maintains discretionary latitude concerning how it exercises it enforcement discretion in such matters (although not unlimited discretion since its decisions cannot be arbitrary, capricious or abuse the Agency's discretion). Nonetheless, Lannett respectfully contends that enforcement action should be deferred with respect to its Morphine Sulfate and Hydromorphone Rx drug products.

The CPG employs a risk-based approach. It delineates six categories of drugs to which it will accord "higher priority to enforcement actions involving unapproved drug products." CPG at pp. 3-4. Understandably, the top two categories are drugs with potential safety risks and "drugs that lack evidence of effectiveness." There are no issues regarding Morphine Sulfate or hydromorphine with regard to either adverse events or concerns that the drugs are not effective. Neither Lannett nor Cody are aware of any adverse events or adverse event reports. Medical students and nurses are trained routinely in the use and effects of morphine. Lannett follows all applicable GMPs, further lowering any risks. Similarly, category nos. 3,4, and 6 do not apply.

That leaves category no. 5 "unapproved new drugs that are also violative of the Act in other ways." However, this category is really intended to signal that when FDA has other concerns about an unapproved drug—such cGMP violations—it may extend enforcement action to include unapproved new drug charges. Here, there have been no such "other concerns." Even Cody has now been reinspected and early cGMP citations have reportedly been addressed satisfactorily.

Finally, the CPG contains another section—"Special Circumstances—Newly Approved Product"—indicating that the Agency is more likely to initiate enforcement action when a product in an unapproved class of products has received approval. Id. at pp. 5-6. With regard to Morphine Sulfate, Roxane received approval of its §505(b)(2) NDA in March 2008. Lannett has begun work on its own application. However, there are drug product differences (e.g., Roxane's drug is diluted at 10 and 20 mg/5 ml v. Lannett's concentrated solution at 20 mg/1ml). Lannett will need some guidance concerning the data expected in an application. During our April 15 meeting, FDA indicated that the appropriate regulatory pathway is a §505(b)(2) NDA, consisting primarily of CMC information, and that the reviewing division would help advise Lannett throughout this process.

Regarding Hydromorphone HCl, the most recent approval for oral tablets appears to be Tyco's ANDA 78-273 in 2007. That approval postdates Lannett's submission of its own ANDAs in 2004 and 2006. There should be no question that Lannett has been pursuing approval of these products actively and in good faith.

V. More Flexible Approach

FDA acknowledges that it maintains the discretion to afford as much or as little of a grace period as it desires on a case-by-case basis. CPG at page 6. The CPG, likewise, identifies factors to be considered in assessing the grace period to allow. Id. None of the factors support the strict and inflexible approach contained in Warning Letters to seven companies issued on March 30, 2009 (and subsequent press releases). In fact, the first factor, whether the product is medically necessary, has now been recognized by FDA as necessitating a different approach for Morphine Sulfate immediate release concentrated solution: allowing up to 180 days following the first approval of this dosage form instead of 60 and 90 days respectively, for the manufacturing and shipment of product to cease. *See* April 9, 2009 FDA letter (Attachment "C"). This approach is reportedly in recognition of

drug shortages and the critical need to maintain availability of this product by desperately and terminally ill patients in palliative care who cannot swallow tablets, maintain sufficient IV flow (or endure the pain of continuous injection), or swallow sufficient liquids. While the shortage may not be as acute for Hydromorphone HCl, a shortage exists due to a nationwide recall of the 2 mg tablets by KV/ETHEX. In any event, Lannett has been actively pursuing approvals for several strengths. Finally, the history of Lannett's Hydromorphone ANDAs, and the collaborative effort, and significant Lannett and FDA resources, expected for the preparation and review of the Morphine Sulfate 505(b)(2) application, all support flexibility and additional enforcement discretion.

FDA initiatives against other unapproved drugs likewise support more leniency and flexibility with regard to Morphine Sulfate. For example, for levothyroxine and digoxin, FDA negotiated timeframes with product manufacturers and FDA sought to persuade companies to submit NDA/ANDAs in a timely manner so as not to disrupt existing product supply. FDA extended the timeframe for application submission to a total of 3 years despite safety concerns regarding drug potency and stability.

VI. Conclusion

Lannett appreciates the opportunity collaborate with FDA, including the opportunity to meet on April 15, 2009. The Company continues to cooperate fully with the agency and is committed to meet FDA objectives in a timely manner while doing its part to avoid market shortages. It is also good public policy for the FDA to interact and compromise with cooperating companies in this context to address differences of opinion and legitimate concerns. In this regard, Lannett respectfully requests that (1) FDA permit immediate-release Morphine Sulfate solution (20 mg/ml) to remain on the market if a §505(b)(2) NDA is prepared and accepted for filing by FDA prior to December 31, 2009; (2) FDA permit Hydromorphone HCl Tablets 2 mg and 4 mg to remain on the market pending reinspection of Cody Labs or review of the API batch records, and approval of previously submitted ANDAs.

Thank you for your consideration of the information and issues raised herein. Please contact either of us with any questions, comments or if we may be of further assistance.

Sincerely,

Donald E. Segal

Marc J. Scheineson
Donald E. Segal
Counsel to the Lannett Company

Enclosures

cc: Arthur Bedrosian, CEO
Deborah M. Autor, Esq.
Donna Katz, Esq.
Ms. Jennifer Devine
Mr. Gary Buehler
Mr. Howard Manresa
Mr. Thomas Gardine

ADMIN/20394754v1

Attachment "A"

Brief Summary of Lannett/Cody Meeting with FDA on April 15, 2009

Attendees:

For Lannett/Cody:

- Arthur Bedrosian, President/CEO Lannett
- Ernest Sabo, VP-Regulatory Compliance- Lannett
- Robin Dornewass, Director-Quality Assurance- Lannett
- Barry Sugarman,* Co-CEO- Cody Laboratories
- Marc Scheineson, Regulatory Counsel, Alston + Bird
- Donald Segal, Regulatory Counsel, Alston + Bird

For FDA:

- Deborah Autor, Director, FDA/CDER/Office of Compliance (OC)
- Jennifer Devine, Associate Director, FDA/CDER/OC/Division of New Drugs and Labeling Compliance (DNDLC)
- Judy McMeekin, Team Leader, FDA/CDER/OC/DNDLC/New Drugs and Labeling Team (NDLT)
- Sakineh Walther, Compliance Officer, FDA/CDER/OC/DNDLC/NDLT
- Steven Lynn, Project Management Officer, FDA/CDER/OC
- Donna Katz, Attorney, FDA/Office of Chief Counsel
- Jouhayna Saliba, Senior Program Management Officer, CDER/Office of New Drugs (OND)/Drug Shortage Staff (DS)
- Andrei Nabakowski, Senior Program Management Officer, CDER/OND/DS
- David Read, Regulatory Counsel, CDER/Office of Generic Drugs
- Paul Teitell, CSO, ORA/ Denver District*
- Elvin Smith, Supervisory CSO, ORA/DEN-DO*
- Ricki Chase, Supervisory CSO, ORA/DEN-DO*
- Howard Manresa, Supervisory CSO, ORA/DEN-DO*
- Nancy Schmidt, CSO, ORA/DEN-DO*
- Steven Carter, Supervisory CSO, ORA/Philadelphia-District*
- Sharon Hertz, Supervisory Medical Officer, CDER/OND/Office of Drug Evaluation II/ Division of Anesthesia, Analgesia and Rheumatology Products*

* By Telephone

The meeting lasted a little more than one hour, beginning with introductions. Without attempting to capture the back-and-forth dialogue, below is a brief summary of the topics and "decisions" reached.

A. Morphine Sulfate

- By letters dated April 9, 2009, FDA extended the period of enforcement discretion with regard to morphine sulfate oral solution 20mg/ml products, until 180 days after any firm receives approval for such a product or if FDA determines that alternative medications become available for the palliative case of patients. During the meeting, FDA (Autor) stated that:

  (a) The 180-day period would not be extended;
  (b) The agency would not say whether an application had been filed or, if so, who filed it.

- Grandfather – Lannett stated that it maintains a historical file and very few, if any, other companies likely do so. FDA did not respond specifically, other than to restate its general skepticism with regard to grandfather status.

- The regulatory pathway recommended by FDA is the 505(b)(2) application. This would likely mimic the recent Roxane approvals (primarily CMC and pharmacokinetic data). An ANDA is not recommended, and this also avoids the necessity for a suitability petition. Lannett is encouraged to contact the Division to discuss an IND.

- If the 505(b)(2) application provides information to support further need for the product to address a new shortage, FDA would strongly consider priority review.

B. Hydromorphone

- FDA (D. Read) acknowledged that there are no remaining issues with respect to the ANDAs (2/4/8 mg.) except for Cody inspectional issues.

- FDA (Denver) does not dispute that Cody essentially "passed" the reinspection in April 2007, but stated that the District needs to review manufacture of API while in production before the inspection is complete. There was some reluctance by Denver to commit to having an inspector at Cody once Cody reports it is in production. However, D. Autor seemed willing to work with the District concerning scheduling the inspection. It

appears that if Cody provides advance notice concerning when it will be in production, the District will either inspect during that time, or inspect the resulting batch records when available.

- The Warning Letters stated that enforcement discretion with regard to Hydromorphone HCl Tablets, 2 mg. and 4 mg., would not be extended beyond 60 days for manufacture, and 90 days for shipment in interstate commerce. FDA did not express a willingness to extend those time frames. However, the history of the ANDAs and Lannett/Cody's active and continuing pursuit of approval may make it more difficult for FDA to take further action under those circumstances.

General observations:

- At no time did FDA raise serious concerns about:

  -The actual safety or effectiveness of either product;
  -GMP compliance of Lannett
  -The good faith of either Lannett or Cody

- The unapproved drugs group seemed, as a general matter, skeptical about the intentions of companies marketing such products. Lannett sought to distinguish itself from those companies evading regulation.

Attachment B

THE

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA

ELEVENTH DECENNIAL REVISION

(U. S. P. XI)

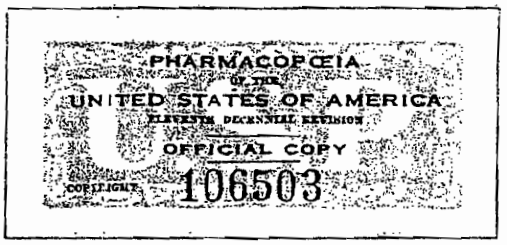
BY AUTHORITY OF THE
UNITED STATES PHARMACOPŒIAL CONVENTION
HELD AT WASHINGTON, D. C., MAY 13 AND 14, 1930

PREPARED BY THE COMMITTEE OF REVISION AND
PUBLISHED BY THE BOARD OF TRUSTEES

OFFICIAL FROM JUNE 1, 1936

AGENT

MACK PRINTING COMPANY
EASTON, PA.



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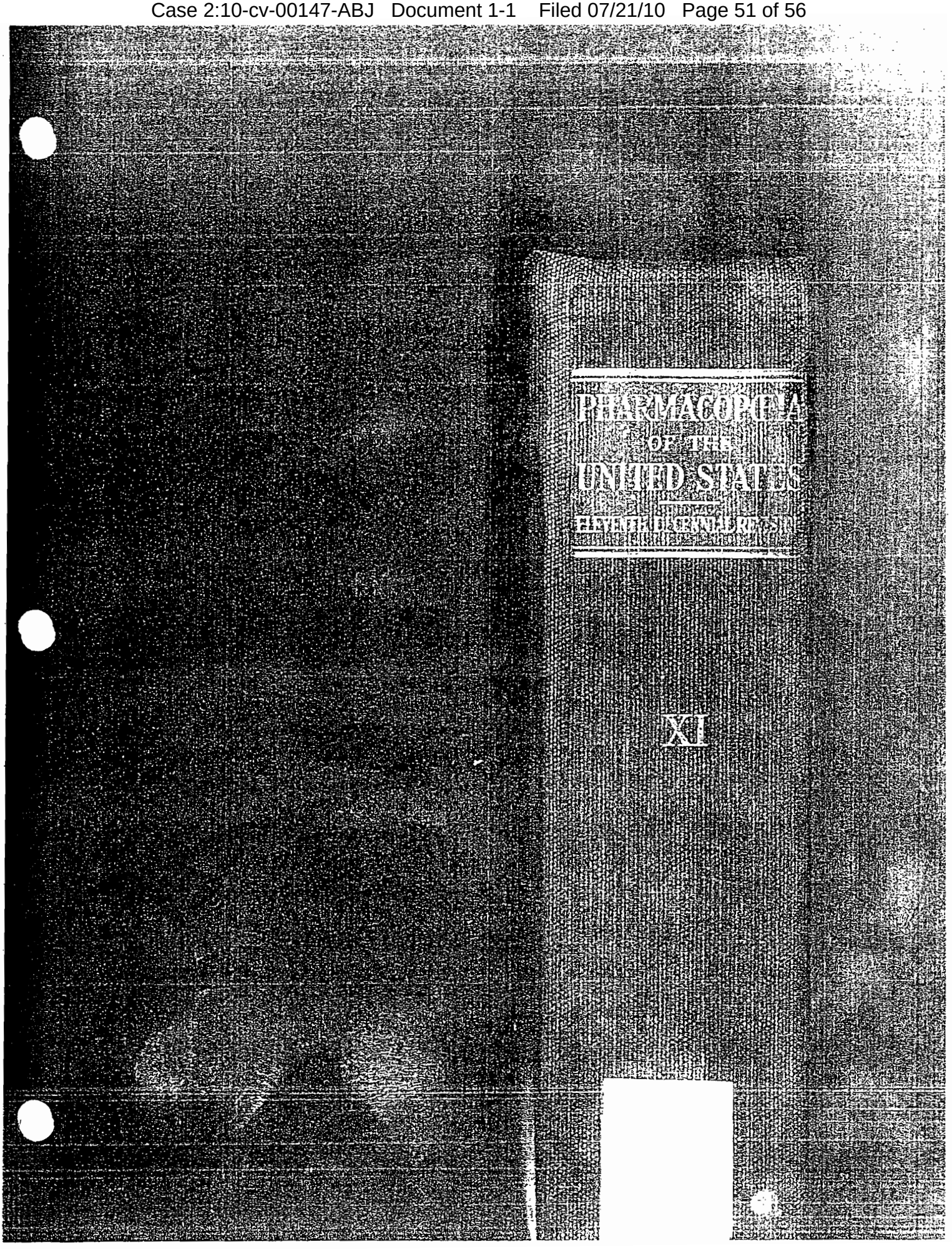

PHARMACOPEIA
OF THE
UNITED STATES
XI

keeping the mixture in constant rotation. Stopper the flask and allow the mixture to stand for fifty minutes, shaking it vigorously at intervals of ten minutes. Add distilled water to make the mixture measure 500 cc., mix thoroughly, allow to stand for ten minutes, and filter through a filter that has not been previously moistened. Reject the first 30 cc. of filtrate. Determine the excess of iodine by titration of 100 cc. of the subsequent filtrate with tenth-normal sodium thiosulfate. Each cc. of tenth-normal iodine is equivalent to 0.005328 Gm. of $C_{16}H_{18}N_3ClS$.

Storage—Preserve Methylthionine Chloride in well-closed containers.

AVERAGE DOSE—Metric, 0.15 Gm.—Apothecaries, 2½ grains.

MISTURA CRETÆ

Chalk Mixture

Mist. Cret.

COMPOUND CHALK POWDER	20 Gm.
CINNAMON WATER	40 cc.
DISTILLED WATER, a sufficient quantity,	
To make	100 cc.

Gradually add the cinnamon water and about 20 cc. of distilled water to the compound chalk powder in a mortar, triturating until the mixture is uniform; transfer this to a graduated vessel, rinse the mortar with enough distilled water to make the product measure 100 cc., and mix thoroughly.

Caution—This preparation must not be dispensed unless it has been recently prepared.

AVERAGE DOSE—Metric, 15 cc.—Apothecaries, 4 fluidrachms.

MISTURA OPII ET GLYCYRRHIZÆ COMPOSITA

Compound Mixture of Opium and Glycyrrhiza

Mist. Opii et Glycyrrh. Comp.—Mistura Glycyrrhizæ Composita U. S. P. X, Compound Mixture of Glycyrrhiza, Brown Mixture

FLUIDEXTRACT OF GLYCYRRHIZA	120	cc.
ANTIMONY AND POTASSIUM TARTRATE	0.24	Gm.
CAMPHORATED TINCTURE OF OPIUM	120	cc.
SPIRIT OF ETHYL NITRITE	30	cc.
GLYCERIN	120	cc.
DISTILLED WATER, a sufficient quantity,		
To make	1000	cc.

Dilute the fluidextract with the glycerin and 500 cc. of distilled water; add the antimony and potassium tartrate dissolved in 12 cc. of hot distilled water, then add the other ingredients, and enough distilled water to make the product measure 1000 cc.

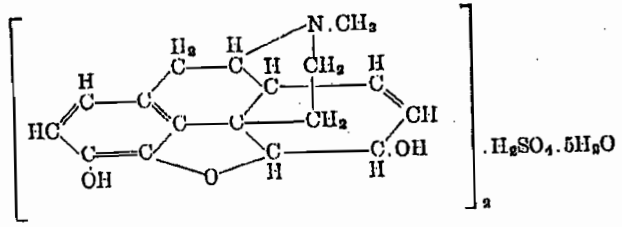
Alcohol content—From 9 to 11 per cent, by volume, of C_2H_5OH.

AVERAGE DOSE—Metric, 4 cc.—Apothecaries, 1 fluidrachm.

MORPHINÆ SULFAS

Morphine Sulfate

Morph. Sulf.



$(C_{17}H_{19}O_3N)_2.H_2SO_4.5H_2O$ Mol. wt. 758.47

The sulfate of the alkaloid morphine.

Description and physical properties—White, feathery, silky crystals, or cubical masses of crystals, or a white, crystalline powder. It is odorless, and is stable in the air.

One Gm. of Morphine Sulfate is soluble in 15.5 cc. of water and in 565 cc. of alcohol, at 25° C. One Gm. is soluble in 0.7 cc. of water at 80° C. and in 240 cc. of alcohol at 60° C. It is insoluble in chloroform and in ether.

Tests for identity—Add a few drops of ammonia T.S. to 5 cc. of an aqueous solution of Morphine Sulfate (1 in 30), and gently shake the mixture: a white precipitate is formed, which dissolves upon the subsequent addition of a few cc. of sodium hydroxide T.S.

Sulfuric acid containing 0.005 Gm. of selenous acid in each cc. gives with Morphine Sulfate a blue color, changing to green and then to brown. (*Codeine* yields a green color, changing to blue and afterward to grass-green.)

Sulfuric acid containing 0.005 Gm. of molybdic acid in each cc. gives with Morphine Sulfate a purple color, changing to blue.

Sulfuric acid containing in each cc. one drop of formaldehyde T.S. yields an intensely purple color with Morphine Sulfate.

With nitric acid Morphine Sulfate produces an orange-red color, fading to yellow.

The addition of a few drops of freshly prepared ferric chloride T.S. to an aqueous solution of Morphine Sulfate (1 in 100) produces a blue color, which is destroyed by acids, by alcohol, or by heating.

Add potassium ferricyanide T.S., containing 1 drop of ferric chloride T.S. in each cc., to an aqueous solution of Morphine Sulfate (1 in 100): a deep blue color is produced at once (difference from *codeine*).

Barium chloride T.S. produces in an aqueous solution of Morphine Sulfate a white precipitate, insoluble in hydrochloric acid.

Tests for purity—The ash from 0.5 Gm. of Morphine Sulfate is negligible, page 439.

A solution of 0.5 Gm. of Morphine Sulfate in 15 cc. of distilled water requires not more than 0.5 cc. of fiftieth-normal sodium hydroxide for neutralization, using 1 drop of methyl red T.S. as the indicator.

Dried to constant weight at 130° C., Morphine Sulfate loses not more than 12 per cent of its weight (*water*).

Warm 0.2 Gm. of Morphine Sulfate with 5 cc. of sodium hydroxide T.S.: the mixture does not evolve a noticeable odor of ammonia (*ammonium salt*).

Add a few drops of ferric chloride T.S. to 5 cc. of an aqueous solution of Morphine Sulfate (1 in 30), previously mixed with 5 cc. of diluted hydrochloric acid: no red color is produced (*meconate*).

Dissolve 1 Gm. of Morphine Sulfate in 10 cc. of sodium hydroxide T.S. in a separator, and shake the solution with three successive portions of 15, 10, and 10 cc. of chloroform, passing the chloroformic solutions through a small filter previously moistened with chloroform. Shake the combined chloroformic solutions with 5 cc. of distilled water, separate the chloroform, and evaporate it carefully to dryness on a water bath. Add to the residue thus obtained 10 cc. of fiftieth-normal sulfuric acid, heat gently until dissolved, cool, add 2 drops of methyl red T.S., and titrate the excess of acid with fiftieth-normal sodium hydroxide: not less than 7.5 cc. of the sodium hydroxide solution is required (*foreign alkaloids*).

Storage—Preserve Morphine Sulfate in well-closed containers, and protected from light.

Average dose—Metric, 0.008 Gm.—Apothecaries, ⅛ grain.

MUCILAGO ACACIÆ

Mucilage of Acacia

Mucil. Acac.—Mucilage of Gum Arabic

Acacia, in small fragments	350 Gm.
Sodium Benzoate	1 Gm.
Distilled Water, a sufficient quantity,	
To make	1000 cc.

Place the acacia in a graduated bottle having a wide mouth and a capacity not exceeding 1000 cc., wash the drug with cold distilled water, allow it to drain, and add enough warm distilled water, in which the sodium benzoate has been dissolved, to make the product measure 1000 cc. After stoppering, lay the bottle on its side, rotating it occasionally, and when the acacia has dissolved, strain the mucilage.

Mucilage of Acacia may also be prepared by adding 400 cc. of distilled water to 350 Gm. of powdered or granular acacia, in a mortar, and triturating until the acacia is dissolved. Then add the sodium benzoate, dissolved in 100 cc. of distilled water, and sufficient distilled water to make the product measure 1000 cc.

Caution—Mucilage of Acacia must not be dispensed if it has become sour or mouldy.

Average dose—Metric, 15 cc.—Apothecaries, 4 fluidrachms.

MUCILAGO TRAGACANTHÆ

Mucilage of Tragacanth

Mucil. Trag.

Tragacanth	6 Gm.
Glycerin	18 Gm.
Distilled Water, a sufficient quantity,	
To make	100 Gm.

Mix the glycerin with 75 cc. of distilled water in a tared vessel, hea the mixture to boiling, discontinue the application of heat, add th tragacanth, and macerate the mixture during twenty-four hours, stir ring occasionally. Then add enough distilled water to make the mix ture weigh 100 Gm., stir actively until of uniform consistence, an strain forcibly through muslin.

MYRISTICA

Myristica

Myrist.—Nutmeg

Myristica is the dried ripe seed of *Myristica fragrans* Houttuy (Fam. *Myristicaceæ*), deprived of its seed-coat and arillode and wi or without a thin coating of lime.

Myristica yields not less than 25 per cent of non-volatile, eth soluble extractive, page 475, and not more than 0.5 per cent of aci insoluble ash, page 473.

Description and physical properties—

Unground Myristica—Ovoid or ellipsoidal, from 20 to 30 mm. in length and ab 20 mm. in thickness; externally light brown to dark brown; reticulat furrowed, the broad end with a large, circular, upraised scar from which ari a groove extending to a depression at the opposite end; the cut surface hav a waxy luster and a mottled-brown appearance; odor characteristically a matic, taste pungently aromatic.

Structure—Perisperm thin, dark brown, penetrating by many wavy branches folds into the yellowish-brown endosperm; embryo small and more or shrunken, in an irregular cavity near the base.

Powdered Myristica—Dark reddish-brown; consisting of irregular yellow brown and blackish-brown fragments; perisperm with large, circular elliptical volatile-oil reservoirs, small thin-walled parenchyma cells w brown contents and occasional spiral tracheæ; endosperm with more or polygonal parenchyma cells containing starch and aleurone grains and o sionally brown pigment; fixed oil globules numerous; starch grains singl 2- to 3-compound, or in aggregates, the individual grains, spherical, pl convex or polygonal, from 0.003 to 0.022 mm. in diameter, with a disti sometimes cleft hilum.

Section III

LISTING OF "PRE-1938" PRODUCTS

The Federal Food, Drug, and Cosmetic Act of 1938 required that drugs be shown to meet certain safety requirements prior to their being marketed. Drugs that were already being marketed at that time were "grandfathered" and were allowed to remain on the market without further regulatory approval if they were labeled with the same conditions of use. Many of these products remain on the market today. Because these products technically have never been *approved* by FDA, they do not appear in the listing of approved drug products with therapeutic equivalence evaluations (the "Orange Book").

The following listing identifies drug products that we believe are considered "pre-1938" or "grandfathered" and are still currently available. The list was developed by comparing an earlier general listing of frequently prescribed "pre-1938" drug entities developed by the U. S. Food and Drug Administration against current dosage form listings in the "Orange Book." The listing is not necessarily complete and comments are welcomed. Additions to or deletions from this list will be shown in future issues of *Update*. The listing of these products should not be interpreted as an attestation by USP as to their actual availability or the general recognition of safety and efficacy of the articles for medical or legal purposes or that a final determination has been made by the FDA.

Acetaminophen, Aspirin, Salicylamide, Codeine Phosphate, and Caffeine
- Tablets

Acetaminophen, Codeine Phosphate, and Caffeine
- Capsules
- Tablets

Amobarbital
- Tablets

Amobarbital Sodium
- Capsules
- Sterile

Amyl Nitrate
- Inhalant

Antipyrine and Benzocaine
- Solution, Otic

Aspirin and Codeine Phosphate
- Tablets

Chloral Hydrate
- Capsules
- Syrup
- Suppositories

Codeine and Calcium Iodide
- Syrup

Codeine Phosphate
- Injection
- Solution, Oral
- Tablets
- Tablets, Soluble

Codeine Sulfate
- Tablets
- Tablets, Soluble

Colchicine
- Injection
- Tablets

Digitoxin
- Tablets

Digoxin
- Elixir
- Tablets

Ephedrine Sulfate
- Capsules
- Injection
- Syrup

Ergonovine Maleate
- Injection
- Tablets

Ergotamine Tartrate
- Tablets

Erythrityl Tetranitrate
- Tablets

Hydrocodone Bitartrate
- Tablets

Hydrocodone Bitartrate, Aspirin, and Caffeine
- Tablets

Hydromorphone Hydrochloride
- Suppositories

Iodinated Glycerol
- Elixir
- Solution, Oral
- Tablets

Levothyroxine Sodium
- Injection
- for Injection
- Tablets

Meperidine Hydrochloride and Acetaminophen
- Tablets

Mephobarbital
- Tablets

Methenamine Mandelate
- for Solution, Oral
- Suspension, Oral
- Tablets
- Tablets (Enteric-coated)

Morphine Hydrochloride
- Suppositories

Morphine Sulfate
- Solution, Oral
- Tablets

Nitroglycerin
- Tablets (Sublingual)

Opium Alkaloids Hydrochlorides
- Injection

Opium Tincture

Oxycodone
- Tablets

Oxycodone Hydrochloride
- Solution, Oral

Paregoric

Pentaerythritol Tetranitrate
- Tablets

Phenazopyridine Hydrochloride
- Tablets

Phenobarbital
- Capsules
- Elixir
- Tablets

Phenobarbital Sodium
- Injection
- Sterile

Pilocarpine Hydrochloride
- Solution, Ophthalmic

Pilocarpine Nitrate
- Solution, Ophthalmic

Potassium Bicarbonate
- Effervescent Tablets for Oral Solution

Potassium Bicarbonate and Potassium Chloride
- for Effervescent Oral Solution
- Effervescent Tablets for Oral Solution

Potassium Bicarbonate and Potassium Citrate
- Effervescent Tablets for Oral Solution

Potassium Chloride
- Solution, Oral

Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate
- Effervescent Tablets for Oral Solution

Potassium Gluconate
- Elixir
- Tablets

Potassium Gluconate and Potassium Chloride
- Solution, Oral
- for Solution, Oral

Potassium Gluconate and Potassium Citrate
- Solution, Oral

Potassium Iodide
- Solution, Oral
- Syrup
- Tablets (Enteric-coated)

Monobasic Potassium Phosphate
- Tablets for Oral Solution

Potassium Phosphates
- Capsules for Oral Solution
- for Solution, Oral

Potassium and Sodium Phosphates
- Capsules for Oral Solution
- for Solution, Oral
- Tablets for Oral Solution

Monobasic Potassium and Sodium Phosphates
- Tablets for Oral Solution

Quinacrine Hydrochloride
- Tablets

Quinine
- Capsules

Quinine Sulfate
- Tablets

Salsalate
- Capsules
- Tablets

Secobarbital Sodium and Amobarbital Sodium
- Capsules

Sodium Fluoride
- Solution, Oral
- Tablets

Thyroid
- Tablets
- Tablets, Enteric-coated

Trikates (Potassium Acetate, Potassium Bicarbonate, and Potassium Citrate)
- Solution, Oral

Attachment C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

April 9, 2009

Arthur P. Bedrosian, J.D., President
Lannett Company, Inc.
9000 State Road
Philadelphia, PA 19136

Product:
Morphine Sulfate Solution Immediate Release 20 mg/ml

Dear Mr. Bedrosian:

This letter is written in reference to the March 30, 2009 warning letter (Warning Letter) your firm received for /distributing morphine sulfate oral solution 20 mg/ml, an unapproved new drug, in violation of the Federal Food, Drug, and Cosmetic Act (the Act).

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to assure that safe and effective drugs are available to the American people. The drug approval system is one of the essential means by which CDER achieves its mission and ensures that patients have access to prescription drugs of proven safety, efficacy, and quality.

FDA remains committed to taking enforcement actions against unapproved drugs in an effort to ensure that drugs used by patients are safe and effective, while at the same time ensuring that such actions do not impose an undue burden on patients. Currently, there are no approved morphine sulfate oral solution 20 mg/ml products being marketed in the U.S. FDA has heard from the pain management community that the impending market removal of unapproved morphine sulfate oral solution 20 mg/ml products announced in the Warning Letter would impose extreme hardship on palliative care patients and their families. In light of this information, FDA intends to extend the period of enforcement discretion set forth in the Warning Letter to ensure that palliative care patients have access to morphine sulfate oral solution 20 mg/ml.

The period of enforcement discretion set forth in the Warning Letter will be extended until 180 days after any firm receives approval for a morphine sulfate oral solution 20 mg/ml product. If your firm [manufacturers/distributes] an unapproved morphine sulfate oral solution 20 mg/ml beyond the date that is 180 days after the date of such an approval, that activity may result in legal action without further notice, including, without limitation, seizure and injunction. The

extension of this period of enforcement discretion will not apply if FDA determines that your firm is violating other provisions of the Act or identifies additional safety information, or if FDA determines that alternative medications become available that could meet the needs of palliative care patients. FDA is actively evaluating alternatives to morphine sulfate oral solution 20 mg/ml and working with firms to expedite approval of such products. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations. Please be advised that we are not extending the period of enforcement discretion for any other products identified in the Warning Letter; the period of enforcement discretion stated in the Warning Letter will continue to apply to those other products.

Furthermore, FDA reiterates its expectation that all firms that market unapproved drugs to the American public submit the required applications to obtain approval for those products. FDA intends to continue to take aggressive enforcement action against marketed unapproved drugs.

FDA understands the need to continue to provide assistance to firms and to help them secure approval for unapproved drugs they are currently marketing. As part of this commitment, FDA appointed an unapproved drugs coordinator in the Office of New Drugs, Dr. Sally Loewke, to work with companies trying to bring their products into compliance. Please contact Parinda Jani, Chief Project Manager, Office of New Drugs, at 301-796-1232, about obtaining the necessary approval for your unapproved morphine sulfate oral solution 20 mg/ml drug product or any other unapproved product you may be marketing.

FDA is committed to making sure that patients have access to drugs of proven safety, efficacy, and quality and hopes that your firm shares this same commitment. If you have any additional questions concerning this letter, please contact Ms. Sakineh Walther, Compliance Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, HFD-310, WO51 RM 542, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration